Type 2 Diabetes Pharmacotherapy

Updated 2023 Treatment Algorithm

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Healthy lifestyle behaviors, self-management education/support and social determinants of health should be considered in all patients.

First-line pharmacotherapy should be selected based upon patient-specific factors: glycemic management needs, cardiorenal risks, comorbidities, cost and access.

Consider **combination pharmacotherapy** at initiation if A1C ≥1.5% above target goal.

Consider **early insulin initiation** with extreme hyperglycemia:
- BG ≥300 mg/dL
- A1C >10%
- Signs of catabolism

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Reassess and modify treatment every **3-6 months**

Established/High-Risk of ASCVD, **Heart Failure**, or **Chronic Kidney Disease**? **No**

Recommended independent of baseline A1C, target A1C goal, or metformin use

ASCVD (established or high risk)

GLP-1 RA or SGLT2i with proven CVD benefit

If A1C above target

- On GLP-1 RA? Consider incorporating SGLT2i with CVD benefit (and vice versa)
- Consider low dose TZD (avoid in patients with HF)

Heart Failure (preserved or reduced EF)

SGLT2i with HF benefit
- Avoid TZDs
- Avoid saxagliptin

If A1C above target

Chronic Kidney Disease (eGFR < 60 mL/min and/or UACR ≥ 30 mg/g)

On maximally tolerated **ACEi/ARB**

SGLT2i with primary evidence for reducing CKD progression
- May be initiated with an eGFR as low as 20 mL/min
- Strongest evidence of benefit when UACR ≥ 200 mg/g
- If SGLT2i therapy is contraindicated or not tolerated, use of a **GLP-1 RA** with CVD benefit is recommended

If A1C above target

On SGLT2i? Consider incorporating GLP-1 RA (and vice versa)

CLASS	ASCVD	HEART FAILURE	RENAL
SGLT2is	**FDA approved CVD benefit:** • canagliflozin • empagliflozin **Neutral:** • dapagliflozin • ertugliflozin	**FDA approved HF benefit:** • dapagliflozin • empagliflozin **Evidence for benefit:** • canagliflozin • ertugliflozin	**FDA approved renal benefit:** • canagliflozin (DKD) • dapagliflozin (CKD) **Evidence for benefit:** • empagliflozin
GLP-1 RAs & GLP-1/GIP RAs GLP-1/GIP RA tirzepatide is under investigation for CV	**FDA approved CVD benefit:** • dulaglutide • liraglutide • semaglutide (SUBQ) **Neutral:** • exenatide ER • lixisenatide • semaglutide (oral)	Neutral	**Evidence for renal benefit:** • dulaglutide • liraglutide • semaglutide (SUBQ)

NOTE: Labeled indications and evidence for individual agents are subject to frequent change and geographic variability. Last updated 12/2022.

Select therapies with **adequate efficacy** to achieve and maintain **treatment goals**.

In patients with concurrent **glycemic management** and **weight management goals**, consider therapies with **high** to **very high** glucose-lowering and weight-loss efficacy.

Glucose-Lowering Efficacy

Very High:
- Dulaglutide (high-dose)
- Semaglutide
- Tirzepatide
- Insulin
- Combination therapy

High:
- GLP-1 RA (not listed above)
- Metformin
- SGLT2i
- Sulfonylurea
- TZD

Intermediate:
- DPP-4i

Weight-Loss Efficacy

Very High:
- Semaglutide
- Tirzepatide

High:
- Dulaglutide
- Liraglutide

Intermediate:
- GLP-1 RA (not listed above)
- SGLT2i

Intermediate:
- DPP-4i
- Metformin

Cost and Access

Add oral options available in generic form/lower cost:
- SU
- TZD*

Consider insulins that are available at lower cost:
- NPH
- Regular

Patient assistance programs may be available for certain brand name medications

*Pioglitazone is available as generical; rosiglitazone is brand only (Avandia)

If A1C above target

Add additional agents based on patient-specific factors including: comorbidities, risks, glycemic management needs, convenience, cost and access

Do not combine DPP-4i, GLP-1 RA and/or tirzepatide (GLP-1/GIP RA)

References: American Diabetes Association. Section 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2023. Individual manufacturer product labels.

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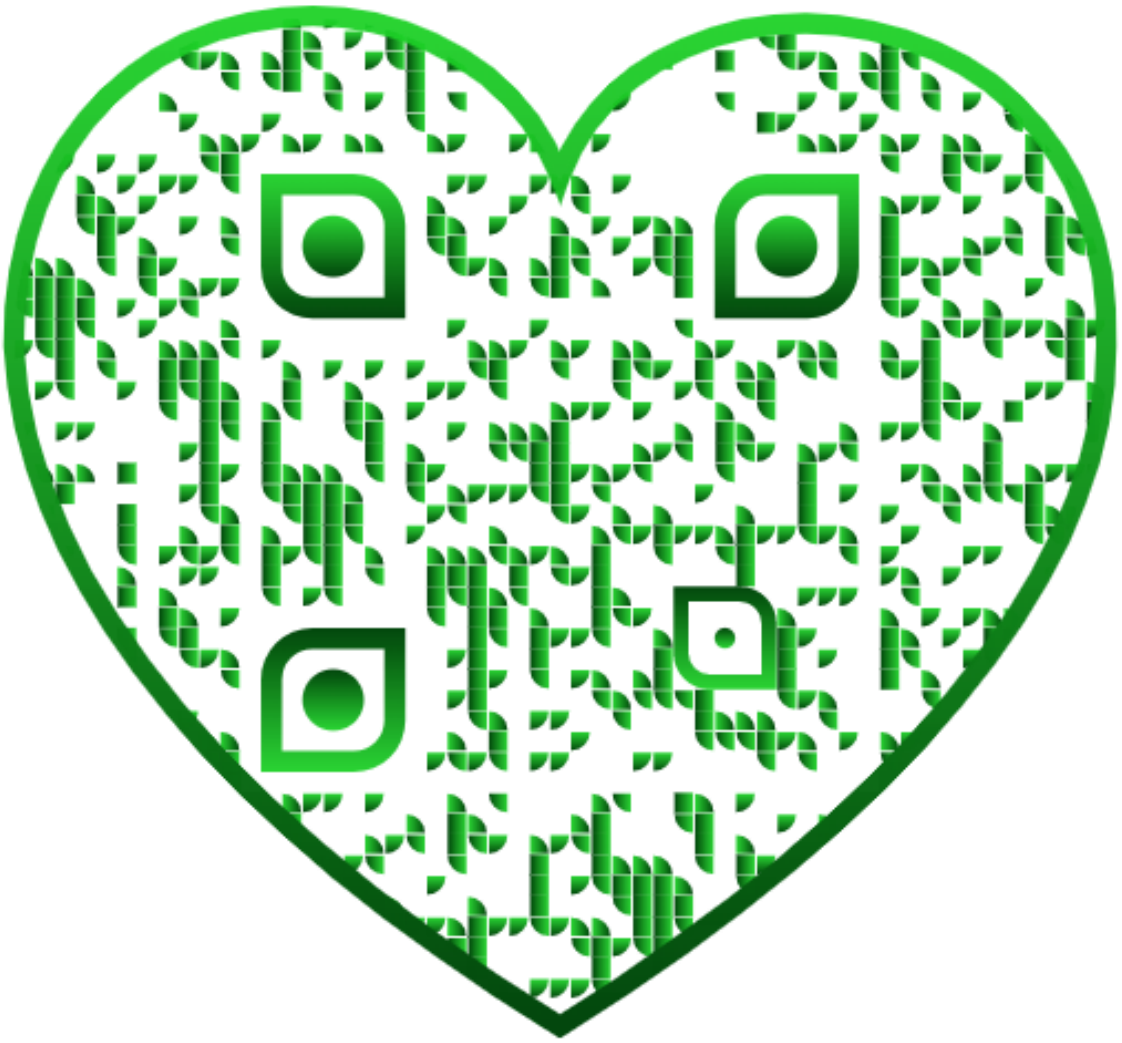

Type 2 Diabetes Pharmacotherapy

Updated 2023 Treatment Algorithm

Comprehensive lifestyle changes and non-insulin agents should generally be considered prior to insulin therapy

Consider **early insulin initiation** with extreme hyperglycemia: BG ≥300 mg/dL, or A1C >10% or signs of catabolism present

See Page 1 regarding non-insulin initial pharmacotherapy use and selection

Reassess and modify treatment every **3-6 months** to avoid therapeutic inertia

Injectable therapy needed to lower A1C?

Consider **GLP-1 RA** or **GLP-1/GIP RA** in most patients prior to insulin
Titrate to **maintenance dose**

Already on **GLP-1 RA** or **GLP-1/GIP RA**?
GLP-1 RA or GLP-1/GIP RA **not appropriate**?
Or is **insulin preferred**?

Assess basal insulin dose adequacy & evaluate for overbasalization

Evaluate for clinical signs of overbasalization or need for adjunctive therapy:
- basal dose >0.5 units/kg
- ↑ bedtime-morning/post-prepandrial differential
- hypoglycemia (aware or not)
- high variability

Add **basal insulin analog** or **bedtime NPH** based upon patient-specific factors (e.g. cost)

START: 10 units/day or 0.1-0.2 units/kg/day

TITRATE to fasting plasma glucose (FPG) target:
- Follow an evidence-based titration algorithm, e.g. ↑ 2 units every 3 days until FPG target
- Hypoglycemia is never acceptable; titrate at a rate to minimize hypoglycemia risk
- If hypoglycemia occurs for no clear reason, ↓ dose 10-20%

If A1C is above target

On bedtime NPH? Consider conversion to BID NPH

One possible approach:

START:
- Total dose = 80% of current
- 2/3 given in the morning
- 1/3 given at bedtime

TITRATION: Titrate based on the individual's needs

Add prandial insulin

Usually start with one dose with the largest meal or meal with greatest PPG excursion; prandial insulin can be dosed individually or mixed with NPH as appropriate

START:
- 4 units/day or 10% of basal insulin dose
- If A1C <8%, consider ↓ basal dose by 4 units/day or by 10% of basal dose

TITRATION:
- ↑ dose 1-2 units or 10-15% twice weekly
- If hypoglycemia occurs for no clear reason, ↓ dose by 10-20%

If A1C is above target

If A1C is above target

Consider BID premix insulin

START:
- Usually unit per unit at the same total insulin dose, but may require adjustment for the individual's needs

TITRATION: Titrate based on the individual's needs

Stepwise additional prandial injections

(i.e. 1 then 2 then 3 injections)

Full basal-bolus regimen

(i.e. prandial insulin w/ meals and basal insulin)

Consider self-mixed/split insulin regimen

Can adjust NPH and short/rapid-acting insulins separately

START:
- Total NPH dose = 80% of current NPH
- 2/3 given before breakfast
- 1/3 given before dinner
- Add 4 units of short/rapid insulin to each injection or 10% of reduced NPH dose

TITRATION:
- Titrate components of the regimen based on the individual's needs

References:
American Diabetes Association. Section 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2023.,
Individual manufacturer product labels.

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